ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Lobelia salicifolia*, Alkaloids of.** E. Steinegger and F. Ochsner. (*Pharm. Acta Helvet.*, 1956, **31**, 97.) The alkaloids of *L. salicifolia* may be separated by paper chromatography. A new compound is given the name salicilobine, and appears to be derived from lobinanine by removal of methyl-ethyl ketone. Other compounds identified were nor-lobelanine, nor-lobelanidine, lobelanine, lobelanidine, (+)- and (−)-lobeline, decomposition products of the alkaloids, a new not-identified alkaloid, and a substance with an acrid taste. G. M.

ANALYTICAL

Deuterisation of Steroids and their Use in Isotope Dilution Analysis. S. L. Jones, I. D. Robinson, B. H. Arison and N. R. Trenner. (*Analyt. Chem.*, 1956, **28**, 482.) This method was developed for the analysis of compound S (17-hydroxy-11-desoxycorticosterone) and compound F (17-hydroxy-corticosterone) in fermentation liquors during the microbial oxidation of compound F to compound S. Deuterium was introduced into the steroid molecule using a platinum catalyst and 70 per cent. deutero-acetic acid (prepared by the action of deuterium oxide on acetic anhydride). Known amounts of deutero compounds F and S are added directly to whole fermentation liquor, intimately mixed, then extracted, separated and purified. The dilution of deuterium in the isolated steroids is found, from which the original steroid content of the broth can be calculated. The steroids are separated by a countercurrent technique, and the deuterium is determined from the infra-red spectrum of the water formed on combustion of the steroids. D. B. C.

Glyceryl Trinitrate Tablets, Analysis of. G. Schwartzman. (*J. Assoc., off. agric. Chem.*, Wash., 1956, **39**, 254.) The infra-red absorption curve of glyceryl trinitrate in carbon disulphide is used for quantitative measurements at 6·05 and 7·90 μ. Samples of tablets were extracted with carbon disulphide and the recorded spectra of the sample and a standard from 2–15 μ were compared to ascertain the identity of the sample; the baseline absorbance of each was then determined at 7·90 μ. Five samples of commercial nitroglycerin tablets were analysed by the proposed method and by the U.S.P. XV assay; the results show good agreement. R. E. S.

Griseofulvin in Fermentation Samples, Determination of. G. C. Ashton and A. P. Brown. (*Analyst*, 1956, **81**, 220.) A physico-chemical procedure for the determination of griseofulvin is described involving extraction of whole-broth samples with butyl acetate and measurement of the ultra-violet spectrophotometric absorption of the extract. Irrelevant ultra-violet absorption in the extract is allowed for mathematically by a correction procedure which is described. Results obtained by an isotope dilution method based on ^{36}Cl griseofulvin are reported by Ashton (*ibid.*, 228) and are compared with those obtained by the spectrophotometric method. D. B. C.

Morphine in *Papaver somniferum*, Ion Exchange Separation of, before Assay. C. H. van Etten, F. R. Earle, T. A. McGuire and F. R. Senti. (*Analyt. Chem.*, 1956, **28**, 867.) In the processing of morphine from poppy plants, the following rapid and accurate method was used:—An aqueous extract was prepared by a suitable extraction process. A sample containing 5- to 20-mg. of morphine in 5- to 50-ml. was passed through a 5 cm. column of Dowex 50 X 1 cation exchanger in the H-form, washed with 5 to 10 ml. of water and eluted with 50 ml. of 0·5N ammonium hydroxide. The eluate was then passed through an anion exchange 6 cm. column of Dowex 1 X 1 Cl in the OH-form which retained the morphine and all the other ampholytes. The column was washed with three × 5 ml. of water and eluted with 50 ml. of 0·3N acetic acid. This eluate was passed through a cation developer 5 cm. column in the Na-form (Dowex 50 X 1 Na). This column was then eluted with a borate buffer of pH 8·6 until the effluent reached this pH, then 30 ml. more buffer was passed through. The morphine-containing fraction was then eluted with 225 ml. of a borate buffer pH 9·4. This eluate, after acidification with 3N hydrochloric acid, was concentrated on a steam bath and then diluted to 50 or 100 ml. From this, samples containing 0·1 to 2·0 mg. of morphine were analysed colorimetrically by the colour produced with nitrous acid, or by ultra-violet absorption. Larger amounts could be isolated and estimated by titration. The average value for recovery of 20 mg. morphine was 98 per cent. with a standard deviation of 1·9. D. B. C.

Organic Nitrogen, Ampoule Combustion—Isotope Dilution Technique for. S. L. Jones and N. R. Trenner. (*Analyt. Chem.*, 1956, **28**, 387.) The principle of isotope dilution is used in this method which can estimate with precision small quantities of elemental nitrogen in organic compounds. The sample (trace, or tracer and unknown) is converted into nitrogen gas by sealing with an excess of cupric oxide in an evacuated ampoule of high-silica glass and heating in a furnace to complete combustion. The ampoule is opened in a previously evacuated ampoule breaker and the combustion gases, after absorption of carbon dioxide and water, are passed into a mass spectrometer where the isotope ratio of the nitrogen is determined. The sample size can be well under 1 mg. An error of ± 0·5 per cent. may be contributed by the background in the mass spectrograph, while the residual nitrogen from the copper oxide and ampoule may contribute another 0·5 per cent. error. Apart from this the accuracy depends upon the weighing of the small samples. D. B. C.

Phenobarbitone, Argentimetric Potentiometric Titration of. J. I. Bodin. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 185.) The method is a modification of a dead-stop end-point method, in which the uncertainty in the end-point potential is eliminated by determining the potential of a standard blank solution just before the titration of each sample. This is necessary because the end-point potential varies from time to time according to the condition of the electrodes. A silver indicator electrode is placed in the solution to be examined and the solution connected by a salt bridge to a saturated calomel electrode. Prior to titration, the potential of a solution containing 10 ml. of ethanol (95 per cent.), 50 ml. of 3 per cent. sodium carbonate solution and 1 ml. of 0·01N silver nitrate with water to 100 ml. is determined. The sample is dissolved in the same solvent (without the silver nitrate) and titrated to the potential of the blank. Good accuracy is reported by this method which is not affected by the usual amounts of excipients, although stearates should be removed before titration, and correction is necessary in the presence of ethanol or hexamine. G. B.

Sugars and Related Substances, Colorimetric Method for. M. Dubois, K. A. Gilles, J. K. Hamilton, P. A. Rebers and F. Smith. (*Analyt. Chem.*, 1956, **28**, 350.) Simple sugars, oligosaccharides, polysaccharides, and their derivatives including the methyl ethers with free or potentially free reducing groups, give an orange-yellow colour when treated with phenol and concentrated sulphuric acid. The reaction is sensitive and the colour is stable. By the use of this phenol-sulphuric acid reaction, a method of estimating 10–70 μg. amounts of sugars and related substances has been developed. In conjunction with paper partition chromatography, a synthetic mixture of sugars can be analysed, and the method is useful for determining the composition of polysaccharides and their methyl derivatives. D. B. C.

Vitamins D_2 and D_3 in Pure Solution, Estimation of. D. H. Laughland and W. E. J. Phillips. (*Analyt. Chem.*, 1956, **28**, 817.) The method is based upon the formation of a coloured reaction product when the vitamins are treated with furfural and sulphuric acid under carefully controlled conditions. The method is applicable to binary mixtures and to samples containing as little as 15 μg. of total vitamin D, regardless of the relative abundance of each. The details are as follows:—Place a 2·0 ml. aliquot (not less than 15 μg. of total vitamins) of an ethanol solution of the vitamins in a 50 ml. centrifuge tube. Add 1·0 ml. of furfural reagent (0·0046 per cent. in 95 per cent. ethanol) and cool the tube by immersion in a mixture of ethanol and dry ice in a Dewar flask. Stir with a fine stream of nitrogen and maintain the temperature at 13° $\pm$ 5° C. by raising or lowering the tube. Add 7·0 ml. of concentrated sulphuric acid dropwise at about 1 ml. per minute. Allow to come to room temperature and determine the absorption curve 20 minutes after commencing to add the acid. Both forms of the vitamin complex absorb at 490 mμ while that of vitamin D_2 shows a subsidiary peak at 565 mμ, and the absorption of the vitamin D_3 complex is neglegible at this wavelength, so that assays of mixtures can be based on the ratio of absorbancies at these wavelengths. Of substances structurally related to the vitamins, only 7-dehydrocholesterol and ergosterol interfere seriously, and all show different absorption curves from those of the vitamin complexes. D. B. C.

BIOCHEMISTRY

BIOCHEMICAL ANALYSIS

Cobalt in Animal Tissues, Estimation of Trace Quantities of. R. G. Keenan and J. F. Kopp. (*Analyt. Chem.*, 1956, **28**, 185.) Two spectrochemical methods for the determination of submicrogram quantities of cobalt in animal tissues have been devised which are more sensitive and less subject to the effect of interfering elements, notably iron, than chemical methods. One method is applied directly to the ash of tissues containing at least 0·025 μg. of cobalt per g. of fresh tissue in excess of that present in normal tissue and was applied to animals exposed to cobalt in the course of an investigation of the toxicity of this element. The other method was developed for the determination of cobalt in normal tissues. This employs the principle of preliminary chemical concentration with 1-nitroso-2-phenol as a complexing agent. The next stage in both methods is the collection of the cobalt in a mixture of aluminium oxide, lithium chloride and graphite which is loaded into the specially prepared crater of a spectroscopically pure graphite electrode of standard dimensions. The

concentration of the cobalt is calculated from standard curves based on photographs of the spectra of known concentrations under identical conditions. For the direct method, the error is ± 10 per cent., while that for the cobalt concentration method is − 6 per cent. D. B. C.

Hæmoglobin in Plasma, Spectrophotometric Determination of Total. K. B. McCall. (*Analyt. Chem.*, 1956, **28**, 189.) All hæmoglobin is first converted to methæmoglobin; the absorbance of this solution is then evaluated before and after a small amount of cyanide is added to convert all the methæmoglobin to cyanmethæmoglobin. The change in absorbance observed is directly proportional to the total hæmoglobin and is calculated directly. The method offers the advantages of simplicity, stable reagents, and the production of stable colours with an acceptable degree of precision. D. B. C.

Nicotine in Urine, Nephelometric Determination of. M. Mokranjac, S. Radmić and E. Galijan. (*Acta Pharm. Jug.*, 1955, **5**, 115.) To 50 ml. of urine add an excess of sodium hydroxide solution and distil until only a few ml. remains. Add to the distillate 25 ml. of water and redistil. Distil once more and extract the distillate with 3 successive quantities of 15 ml. of ether. Mix the ethereal solutions, add 5 drops of 0·5 per cent. hydrochloric acid to prevent loss of nicotine by volatilisation and evaporate the ether. To the residue add 5 drops of modified Sonnenschein reagent (phosphomolybdate in nitric acid) and dilute to 3 ml. with water. Compare the optical density of the suspension obtained with that of suspensions prepared from known quantities of standard nicotine solution in the same way and hence calculate the quantity of nicotine in the urine. Samples containing 25 to 500 μg. of nicotine may be assayed by this method. G. B.

Vitamin A, Slope-Ratio Liver-Storage Bioassay for. S. R. Ames and P. L. Harris. (*Analyt. Chem.*, 1956, **28**, 874.) Five groups of depleted rats were supplemented as follows: two levels of the reference standard (1000 and 2000 units), two similar levels of test material, and a negative-control group. The relative potency is determined by the ratio of the slopes of the two linear dose-response lines. The liver-storage of vitamin A showed an essentially linear response over a dose range of 500 to 10,000 units. Direct comparison of the results of this method and that of growth response showed no significant difference. After depletion and feeding, details of which are given, the animals are killed and the entire livers are removed, blotted, weighed and stored at − 15° C. until analysed. Each rat liver is ground in a mortar with anhydrous sodium sulphate until dry, extracted with peroxide-free anhydrous ether, and after removal under nitrogen of the ether from an aliquot part of the extract, the intensity of the blue colour formed on the addition of antimony trichloride is measured in a suitable colorimeter using a 620 mμ filter, and the result estimated from a standard curve. Full details of statistical analysis are given. The standard error of the assay is less than ± 10 per cent. D. B. C.

PHARMACY

NOTES AND FORMULÆ

Agars, Determination of the Grade Strength of. N. R. Jones. (*Analyst*, 1956, **81**, 243.) The proposed method is based on a determination of the percentage of agar necessary to produce an agar-water jelly of a given strength when prepared under standard conditions. The standard jelly strength chosen is

one of 75 g., for a deflection of 20° on the F.I.R.A. jelly tester (i.e., that of the Food Industries Research Association obtainable from Messrs. H. A. Gaydon and Co. Ltd., Croydon, Surrey). The jelly tests are made at two concentrations of agar (0·5 and 1·0 per cent.) and the concentration required to produce a jelly strength of 75 g. is found by interpolation. The grade strength is conveniently expressed as the number of grams of jelly of the standard strength obtainable from 1 g. of agar. D. B. C.

PHARMACOLOGY AND THERAPEUTICS

Acetyl-Digitoxin, Clinical Experience with. M. Goldfarb, M. C. Thorner and G. C. Griffith. (*Amer. J. med. Sci.*, 1956, **231**, 186.) Acetyl-digitoxin is a new cardiac glycoside prepared from *Digitalis lanata* by removal of one glucose molecule from lanatoside A. It has been studied in 82 patients over periods up to eight months. It acts quickly and it is completely absorbed from the gastrointestinal tract. In congestive heart failure it decreases heart size and rate and produces a marked diuresis. Initial digitalization was obtained with a total dose of 1·8–2·4 mg. (0·6–0·8 mg in three four hour doses), and the maintenance dose was from 0·1–0·2 mg. daily. Signs of toxicity were seen in one-fifth of the patients, untoward effects being nausea, vomiting, diarrhœa, blurred vision, headache and premature ventricular contractions. These effects are prevented by decreasing the dose. It is suggested that acetyl-digitoxin is indicated in all forms of congestive heart failure, in uncontrollable atrial fibrillation, paroxysmal tachycardia and atrial flutter. G. F. S.

Angiotonin and (—)-Noradrenaline, Relation of, to Essential Hypertension. S. E. Greisman. (*J. exp. Med.*, 1956, **103**, 477.) If a humoral pressor substance is responsible for essential hypertension in man, one of its characteristics should be the ability to constrict the arteriolar bed sufficiently to increase the total peripheral resistance, but not sufficiently to reduce the cutaneous blood flow. This hypothetical pressor substance should also be capable of producing a generalised systemic arteriolar constriction without inducing significant constriction or decreased blood flow in a cutaneous capillary bed such as the nailfold. The purpose of this work is to determine the reaction of the nailfold bed in persons made hypertensive by the infusion of angiotonin and to compare this reaction with that seen in persons with hypertension induced by noradrenaline and in persons with essential hypertension. Such observations indicate that angiotonin, unlike noradrenaline, is capable of raising the systemic arterial blood pressure without inducing sustained ischæmia of the nailfold capillary bed. Evidence was also obtained that the nailfold bed of persons made hypertensive by the intravenous infusion of angiotonin exhibited a hyper-activity to circulating noradrenaline, similar to that found in patients with essential hypertension. From these results it seems that angiotonin is a substance which possesses the properties required of the hypothetical substance of essential hypertension. M. M.

Cerebral Tissue Extracts, Spasmolytic Effects of. O. C. Forbes. (*Nature, Lond.*, 1956, **177**, 893.) Previous work has shown that contractions of the guinea-pig ileum caused by acetylcholine or by adenosine triphosphate can be antagonised with extracts of rat brain. Using an extract of dried red-cell stroma, there was relaxation of the acetylcholine responses but not of the adenosine triphosphate contractions. An investigation was then carried out into the possible presence of a relaxing agent other than choline esterase in brain extracts. An extract of cow brain consisting of crude sphingosine bases

was found to abolish the acetylcholine and the adenosine triphosphate responses of the guinea-pig ileum, similarly to whole brain extracts. Using the Trendelenburg preparation, this extract abolished the peristaltic movement of the ileum. A more purified fraction (triacetylsphingosine) showed qualitatively similar effects. Thus sphingosine and allied bases in cerebral tissue may exert a powerful spasmolytic action *in vitro*. M. M.

Cortisone, Effect of, on Blood. T. Nicol and D. L. J. Bilbey. (*Nature, Lond.*, 1956, **177**, 524.) The phagocytic activity of the reticulo-endothelial system is depressed during the first two weeks of cortisone treatment, activity returning to normal levels during the third and fourth weeks of treatment. Changes have now been shown to occur in the blood from guinea-pigs given 10 mg. cortisone daily by intramuscular injection for five weeks. Blood was removed by heart puncture before the start of treatment and thereafter at the end of each week. Blood films were stained with Giemsa stain. During the first two weeks of treatment the degree of polychromasia and anisocytosis increased above normal levels. At the end of the second week immature red cells were present in greater numbers, although the red-cell count remained unaltered; the hæmoglobin-level fell from 81 to 70 per cent. The total leucocyte count dropped below normal during the first three weeks of treatment, but rose above normal during the fourth and fifth. The differential white cell count showed a sustained fall in lymphocytes during cortisone administration; pseudo-eosinophils on the other hand gradually increased in numbers. G. P.

Cortisone, Effect of, on the Reticulo-endothelial System. T. Nicol and R. S. Snell. (*Nature, Lond.*, 1956, **177**, 430.) In a previous communication (*Nature, Lond.*, 1954, **174**, 554) the authors have shown that cortisone depressed the activity of the reticulo-endothelial macrophages, particularly in the spleen, and suggested that the lowered resistance to infection shown by patients undergoing cortisone treatment resulted from decreased macrophage activity. In the present communication the results have been extended in dose range of cortisone and duration of treatment. 79 male guinea-pigs received daily injections of trypan blue subcutaneously for six days before being killed by chloroform. Seven of the animals were used as controls, the others received daily intramuscular injections of 5, 10 or 25 mg. of cortisone for a period of 1, 2, 3 or 4 weeks. The uptake of dye by the macrophages of the spleen, liver, and lymph nodes was markedly lower in the animals treated for one to two weeks with cortisone than in the control animals. This depressant effect was seen earlier in animals given the larger doses of cortisone. After cortisone treatment for three or four weeks, dye uptake by the macrophages was the same in treated animals as in the controls. This suggests that patients should be specially protected from intercurrent infection during the early stages of cortisone treatment. G. P.

Cortisone, Effect of, on the Serum Gamma-Globulin. R. S. Snell and T. Nicol. (*Nature, Lond.*, 1956, **177**, 578.) This paper deals with the effect of cortisone on the antibody level in the serum. The serum γ-globulin is taken as a measure of the antibody level since most antibodies are found in association with the γ-globulin fraction of the serum protein. The estimation was made by first separating the γ-globulin by paper electrophoresis, treating the paper with dyes and estimating the optical density of the protein dye complex by means of a photoelectric cell. By this means the percentage of γ-globulin in relation to the total serum protein could be assessed. Male guinea-pigs were used.

Blood samples were taken from each animal by heart puncture and the γ-globulin level estimated as described above. Each animal was then given a daily dose of 10 mg. of cortisone intramuscularly for five weeks. Blood samples were taken at weekly intervals. It was found that in all the animals there was a marked reduction of the γ-globulin level during the first two weeks of the injections and that subsequently it remained at a low level. These results emphasize the profound depression of the body defences by cortisone and the great necessity to protect patients from intercurrent infection especially during the early stages of cortisone therapy. M. M.

Dichloralphenazone and Chloral Hydrate, Comparison of. W. B. Rice and J. D. McColl. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **43**, 137.) Chloral hydrate and dichloralphenazone were tested for acute toxicity in mice, for chronic toxicity and hypnotic activity in rats, for onset and duration of hypnotic activity in guinea-pigs, for analgesic action in mice and for antipyretic action in rabbits. The two compounds were found to be similar in activity and toxicity when considered on the basis of chloral content. Slightly more chloral was required to produce hypnosis when used in the form of dichloralphenazone, but the ratio of lethal and hypnotic doses was approximately the same. The analgesic effect of dichloralphenazone appeared to be due mainly to the phenazone content. Dichloralphenazone has the advantage of ease of handling, being a stable crystalline compound, free from unpleasant odour and taste, and may be used in place of chloral hydrate. G. B.

Dimethylaminoethanol, Synthetic Esters of, Exhibiting Positive Inotropic Cardiac Activity. F. C. Uhle, B. A. Mitman and O. Krayer. (*J. Pharmacol.*, 1956, **116**, 444.) The erythropleum alkaloids, which, like the cardiac glycosides, improve the competence of the failing mammalian heart, have been shown to be β-dimethylaminoethyl or β-methylaminoethyl esters of α,β-unsaturated tricyclic hydroaromatic acids of otherwise unknown structure. While hydrolytic cleavage of the alkaloids leads to totally inactive carboxylic acids, the alkanolamines still retain the qualitative actions of the parent alkaloid, although greatly diminished in potency. Twenty-six esters of one of these alkanolamines, dimethylaminoethanol, with aliphatic, aromatic and α,β-unsaturated carboxylic acids were prepared and tested for this activity in conditions of failure of the Starling heart-lung preparation of the dog, failure being induced by sodium pentobarbitone. Only the difunctional esters of succinic, glutaric, adipic, and pimelic acids had positive inotropic activity—of the order of five to ten times that of the parent alkanolamine. The esters of azelaic and sebacic acids had negligible activity; the esters of some of the other acids, particularly of complex polynuclear acids, caused irregularities of rate and rhythm. G. P.

Ethylmethyl-*iso*octenylamine (EMOA), a New Parasympathetic Ganglionic Blocking Agent. E. G. Pardo, I. Méndez, R. Vargas, J. Cato and J. Laguna. (*J. Pharmacol.*, 1956, **116**, 377.) Of the tertiary amine derivatives of Octin (methyl-*iso*octenylamine) the *N*-ethyl analogue (EMOA) was a more potent spasmolytic agent on the isolated intestine of the rabbit than were Octin, ephedrine, papaverine and diethylmethyl-*iso*octenyl amine (DEMOA). In dogs, stimulation of gastric secretion by histamine was inhibited after intraduodenal or intravenous administration of EMOA; minimal intraduodenal doses having this action had no effect on blood pressure. EMOA had a vasodepressor action in anæsthetised cats, the magnitude and duration

of the fall depending upon dose. The cardiac response to vagal stimulation was blocked by doses causing an appreciable fall in blood pressure; the vasodepressor action of acetylcholine was, however, unaffected. Also, the normal fall in pressure with tetraethylammonium (TEA) or hexamethonium was absent after these doses of EMOA, in some cases TEA causing a rise in pressure after EMOA; on the other hand, TEA had no effect on the action of EMOA. Neither neuromuscular transmission nor transmission through the superior cervical ganglion in the cat was blocked by relatively large intravenous doses of EMOA, but the compound caused a moderate, sustained contraction of the nictitating membrane. Cardiac output in the cat heart-lung preparation was greatly reduced, with only a slight decrease in heart rate. Toxicity of the drug in mice by both oral and intraperitoneal routes was relatively low. There was a slight stimulation of the central nervous system with the compound. The effects of EMOA were interpreted in the main as a selective action on parasympathetic ganglia; in addition, the drug had a direct action on the heart and slight sympathomimetic activity. G. P.

Ethyl 4-Phenylpiperidine-4-carboxylates, *N*-Substituted, Analgesic Action of. R. A. Millar and R. P. Stephenson. (*Brit. J. Pharmacol.*, 1956, **11**, 27.) A series of pethidine derivatives, in which the *N*-methyl group has been replaced by a tertiary amino alkyl group, has been tested for analgesic activity in rats by the tail pressure method of Green and Young. The best compound was morpholinoethylnorpethidine which was three to seven times more active than pethidine. Substitution of S for O in the morpholino ring reduced activity to one-third, and lengthening or shortening the chain of C atoms linking the nitrogen atoms of the two rings considerably reduced activity. Branching also reduced activity. Unlike pethidine the compound did not induce convulsions in mice, but it caused a Straub tail reaction. In spite of its higher analgesic activity the toxicity of this compound was not greater than pethidine to mice. Its analgesic actions were antagonised by nalorphine. G. F. S.

Hydroxy*iso*phthalic Acids, Antipyretic and Analgesic Properties of. H. O. J. Collier and G. B. Chesher. (*Brit. J. Pharmacol.*, 1956, **11**, 20.) 4-Hydroxy-*iso*phthalic acid (4-HIPA) and 2-hydroxy*iso*phthalic acid (2-HIPA), byproducts of the Kolbe-Schmitt process for the manufacture of salicylic acid, have been shown to have an antipyretic action, at least as great as aspirin, in rabbits treated with Proteus pyrogen. Single large intraperitoneal doses of both compounds raised the pain threshold of rats to pressure applied to the tail, and the analgesic activities were greater than aspirin but less than salicylamide and codeine. Analgesia was not accompanied by loss of righting reflex, drowsiness or other visible side effects. The analgesic activity of 4-HIPA was not antagonised by nalorphine, but it was potentiated by codeine, methylpentynol, pentobarbitone and thiopentone. 4-HIPA had a very slight local anæsthetic action. Acute experiments in rats showed that both 2-HIPA and 4-HIPA were less toxic than codeine, aspirin and salicylamide. Subacute and chronic toxicity tests of 4-HIPA showed it to be similar in toxicity to aspirin. 0·2 per cent. of 4-HIPA in the diet of young rats produced only a very slight depression of growth. G. F. S.

5-Hydroxytryptamine, Estimation of, in the Presence of Adrenaline. J. D. Garven. (*Brit. J. Pharmacol.*, 1956, **11**, 66.) The isolated œstrous uterus of the rat contracts to 5-HT but the response is inhibited by adrenaline and noradrenaline, which may be present in some tissue extracts making the assay results

too low. This paper describes the use of mushroom juice, which contains a polyphenoloxidase enzyme, for the elimination of the interference. The tissues were double extracted with acetone which leaves substance P in the insoluble residue. The extracts were filtered and evaporated to dryness at 30 to 35° C. under reduced pressure. One ml. of water was then added to the residue and the solution extracted twice with light petroleum to remove lipids. The aqueous residue was evaporated to dryness under reduced pressure. For the assay, the residue was dissolved in water and treated with a prepared mushroom juice for forty minutes at room temperature. The solutions were then assayed for 5-HT activity in the usual way. Using this method the 5-HT content was determined in a whole series of rabbit tissues. Significant amounts of 5-HT were found in the spleen, various areas of the gut mucosa, blood and serum. The hypothalamus, liver and bone marrow showed smaller amounts. Other tissues (lung, thyroid, pancreas and diaphragm) contained little 5-HT and none was detected in skeletal muscle, nerve and adrenals. The specificity of the extract activity was determined by treatment with lysergic acid diethylamide. G. F. S.

Iproniazid, Mechanism of Drug Potentiation by. J. R. Fouts and B. B. Brodie. (*J. Pharmacol*, 1956, **116**, 480.) Iproniazid (Marsilid or 2-*iso*propyl-1-*iso*nicotinyl hydrazine), a substance with practically no sedative action, prolonged the hypnotic activity of hexobarbitone in mice by inhibiting its metabolic degradation; mice given 50 mg./kg. of iproniazid intraperitoneally in addition to a hypnotic dose of hexobarbitone slept about three times as long as controls given only the barbiturate. The rate of metabolism of the hexobarbitone was estimated by homogenising animals killed either twenty minutes after administration of the drugs or at the point of awakening; at twenty minutes the concentration of hexobarbitone was twice as high in the iproniazid-treated mice as in mice receiving the hexobarbitone alone. However, at the point of awakening, the concentrations of barbiturate were approximately the same in treated and untreated animals. Also, once awakened, the mice could not be returned to sleep with large doses of iproniazid, confirming the indirect action of the prolonging agent. Iproniazid inhibited the oxidative enzyme systems in liver microsomes which oxidise the side chain of hexobarbitone, dealkylate aminopyrine, deaminate amphetamine and hydroxylate acetanilide. Its action is therefore similar to that of β-diethylaminoethyl diphenylpropylacetate (SKF 525-A) and 2:4-dichloro-6-phenylphenoxyethyl diethylamine (Lilly 18947). The way in which the inhibition is occasioned is unknown, but is presumably not due to an interchange of the iproniazid with the nicotinamide moiety of di- or tri-phosphopyridine nucleotide. All three inhibitors, despite dissimilarity of structure, probably act by the same mechanism. G. P.

Lysergic Acid Diethylamide, Tolerance to the Pyretogenic Action of. J. W. Gogerty and J. M. Dille. (*J. Pharmacol.*, 1956, **116**, 450.) Tolerance to administration of lysergic acid diethylamide (LSD-25) has been reported in patients after seven days' treatment with the drug (H. F. Isbell and others, *Fed. Proc.*, 1955, **14**, 354). A similar tolerance to the pyretogenic effect of LSD-25 developed in rabbits with daily administration of 50 μg./kg. intravenously for a period of four to five days. Complete abolition of the response was not obtained in this time, but the effect was greatly reduced. The tolerance persisted for up to nine days after withdrawal of the treatment schedule. G. P.

Nystatin; Effect on Growth of *Candida albicans*. A. J. Childs. (*Brit. med. J.*, 1956, **1**, 660.) This investigation was carried out to see if the simultaneous administration of nystatin to patients receiving tetracycline would have any

effect on the overgrowth of *C. albicans*. The patients studied were 50 males, whose ages ranged from 12 to 81 years, suffering from pneumonia. They had not been treated with adequate chemotherapy prior to admission. The patients were allocated alternately to treatment either with tetracycline alone or with tetracycline plus nystatin. Both groups were given tetracycline orally in a dosage of 0·25 g. four-hourly for 48 hours, after which the dose was reduced to 0·25 g. six-hourly for a further 3 days. In the second group, in addition to the tetracycline, nystatin was given orally, the dose being one tablet, containing 500,000 units, eight-hourly. The frequency with which *C. albicans* occurred in throat swabs, rectal swabs and sputum was observed before, during and after treatment in both groups. Examination of admission specimens showed that *C. albicans* was present in 26 per cent. of all rectal swabs, 24 per cent. of all throat swabs, and 38 per cent. of all sputa. Treatment with tetracycline caused an increase in the number of specimens from which *C. albicans* could be isolated; there was a gradual rise up to the seventh day in hospital. When nystatin was added to the tetracycline the culture results were not uniform but there seemed to be a tendency towards lower yields. In rectal swabs there was a definite trend towards elimination of heavy growths. In throat swabs the effect was less obvious, though no marked rise occurred. So far as the sputum was concerned the two treatment groups seemed to be similar. These results are in keeping with the view that nystatin does not appear in the blood stream in adequate concentration and that it might be ineffective in the treatment of systemic infection. S. L. W.

Oxytocin, Clinical Trial of. H. H. Francis and W. J. A. Francis. (*Brit. med. J.*, 1956, **1**, 1136.) Synthetic oxytocin (Syntocinon containing 10 international units per ml.) has been compared with purified natural oxytocin (Pitocin) in thirty-one patients near term or in labour. The solutions were administered by continuous drip in 5 per cent. dextrose solution at strengths of 2·5, 5, or 10, I.U. per litre. The dose was regulated by the rate of infusion according to the uterine response. Uterine contractions were recorded by a Lorand tocograph, observations being restricted to the first and second stages of labour. The results showed Syntocinon to be strongly oxytocic in all cases and the type, amplitude and frequency of uterine contractions to be indistinguishable from the same dose of Pitocin. The synthetic product was free from undesirable side effects, except for a slight pressor activity too slight to contraindicate its use in therapeutic dosage. G. F. S.

Oxytocin, Synthetic. M. N. Bainbridge, W. C. W. Nixon, H. O. Schild and C. N. Smyth. (*Brit. med. J.*, 1956, **1**, 1133.) Synthetic oxytocin (Syntocinon), standardised biologically to be equal to the international standard preparation, has been studied clinically on the human uterus. Comparative assays were made with oxytocin, using the action on the corpus and cervix uteri of patients undergoing therapeutic abortion, the action on the uterus of patients in labour and the action upon the uterus in post-partum patients on the second or third day after delivery. The results showed that there were no qualitative or quantitative differences between the two preparations. G. F. S.

Sodium 3:5-Diacetamido-2:4:6-triiodobenzoate (Hypaque Sodium), a New Urographic Contrast Medium, and Related Compounds, Toxicity of. J. A. Hoppe, A. A. Larsen and F. Coulston. (*J. Pharmacol.*, 1956, **116**, 394.) The toxicity of a series of 3:5-diacylamino-2:4:6-triiodobenzoic acids was determined for the mouse, rat, rabbit, cat and dog. The least toxic of the series

(ABSTRACTS—*continued on page 816.*)

diagrams of specific pieces of apparatus. Throughout the book much useful information has been compressed by tabulating methods of experiment and physical constants, and also by the use of graphs. The book is excellently referenced, covering the literature up to 1955, though many of the more important methods are described in such detail as not to require further reference. The value of the information contained in this volume outweighs any disadvantage arising from a German text.

J. B. STENLAKE.

(ABSTRACTS *continued from page 814.*)

was sodium 3:5-diacetamido-2:4:6-triiodobenzoate, sodium diatrizoate; acute intravenous LD50 values for the species mentioned were between 11·3 and 14 g./kg. With acutely lethal doses of the drug, death occurred between a few minutes and three hours as a result of massive pulmonary hæmorrhage and consequent right heart failure. Local tissue toxicity was very low as judged by the absence of injury to the tunica intima of the marginal ear vein of the rabbit with repeated injections of a 50 per cent. solution of the salt. In doses of 0·5 to 2·0 g./kg., sodium diatrizoate had no consistent effects on blood pressure, heart rate or respiration in the cat or dog; ganglionic transmission through the cat superior cervical ganglion and the response to serial carotid occlusion in the dog were likewise unaffected. The drug was well tolerated by rats when given intravenously in five consecutive daily doses of 0·5 and 2·0 g./kg.; under the same conditions 4·0 g./kg. caused one death and renal tubular nephrosis in five out of nine rats. In monkeys, sodium diatrizoate was well tolerated at three successive doses of 0·5, 1·0 and 2·0 g./kg. No significant hæmatological or histological changes were observed with these doses. Clinical studies on the drug have demonstrated excellent visualisation of the urinary tract, with low incidence of minor side effects. G. P.

Tryptophan and 5-Hydroxytryptamine in Patients with Malignant Carcinoid, Studies on. S. Udenfriend, H. Weissbach and A. Sjoerdsma. (*Science*, 1956, **123**, 669.) Patients suffering from metastatic malignant carcinoid, a relatively rare disease, show symptoms of intestinal hypermotility, bronchospasm, vasomotor disturbances and cardiac lesions. Blood levels of 5-hydroxytryptamine (5-HT) in these patients were from 0·6 to 3·0 μg./ml. compared with 0·1 to 0·3 μg./ml. in normal subjects. Urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, was 70 to 800 mg./day in carcinoid patients compared with 2 to 9 mg./day in normal controls; this feature was diagnostic of the disease. After administration of 2-^{14}C DL-tryptophan to three of the patients the excretion of labelled 5-HIAA demonstrated that tryptophan is the precursor of 5-HT and its metabolites. With a daily intake of 500 mg. of tryptophan, as much as 60 per cent. was converted to 5-hydroxyindoles, whereas in normal subjects only 1 per cent. was metabolised in this way. Nitrogen balance was just maintained in the carcinoid patient with daily amounts of tryptophan three to four times those required for balance in normal subjects. The altered tryptophan metabolism in the carcinoid patients results in less of the amino-acid being available for normal body requirements, with subsequent weight loss and hypoproteinæmia; pellagra has also been reported in some cases. The disease symptomatology is probably related both to this tryptophan deficiency and to 5-HT excess. G. P.